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Brief Clinical Report

Heterogeneity in Adducted Thumbs Sequence

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We report on a boy with adducted thumbs, microcephaly, swallowing difficulties, hypotonia, and severe mental retardation, but without craniostenosis or arthrogryposis. An MRI scan showed myelinization according to age and mild ventricular enlargement. A muscle biopsy documented irregular-shaped and swollen mitochondriae, but results of mitochondrial function tests were normal. The clinical findings were consistent with a developmental defect of the central nervous system. We include a brief review of the 9 reported cases with adducted thumbs sequence. Am. J. Med. Genet. 70: 114–117, 1997.

KEY WORDS: adducted thumbs; mental retardation; microcephaly; hypotonia

INTRODUCTION

An adducted thumbs syndrome was first described by Christian et al. [1971] as an autosomal-recessive malformation syndrome of flexed and adducted position of the thumbs, arthrogryposis, dysmyelination, craniostenosis, cleft palate, swallowing difficuties, and microcephaly. Several additional cases have been published [Fitch and Levy, 1975; Majoor-Krakauer and Weicker, 1981; Kunze et al., 1983]. To the best of our knowledge, 9 patients have been described so far.

We report on a child with adducted thumbs, microcephaly, swallowing difficulties, hypotonia, and severe mental retardation, who had neither craniostenosis nor arthrogryposis. An MRI scan showed only mild ventricular enlargement but no dysmyelination. A muscle biopsy showed mitochondrial abnormalities. We suggest that this case extends the spectrum of adducted thumbs sequence.

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CLINICAL REPORT

The patient was born at term after a normal pregnancy and delivery. Apgar scores were 9 and 10 at 1 and 5 min, respectively. The parents are nonconsanguineous young and healthy Ashkenazi Jews. Birth weight was 2,985 g, and head circumference was 31 cm (>2 SD below the mean).

Severe feeding problems were evident during the first months of life, with rejection of breast-feeding. Multiple changes in formula did not improve the patient's weight gain. Regurgitation and vomiting were noted at age 2 months, and at age 5 months a feeding tube was inserted. At that time he was a malnourished infant with developmental delay, hypotonia, head lag, and a persistent asymmetric tonic neck reflex. An upper gastrointestinal series and endoscopy showed gastroesophageal reflux. Vomiting could not be controlled by conservative measures, and a gastrostomy was performed at age 1 year. Physical therapy was initiated for general hypotonia at Tel Aviv Medical Center.

An initial evaluation at the child development center was carried out at age 16 months because of psychomotor delay, hypotonia, and microcephaly.

Clinical Examination

Clinical examination showed a well-nourished, gastrostomy-fed infant with microcephaly (head circumference: 43.5 cm), and a hypotonic face with micrognathia, microstomia, a high-vaulted palate, and apparently low-set ears. His palpebral fissures were almond-shaped with epicanthal folds (Fig. 1). He had adducted thumbs (Fig. 2), coxa valga, partial syndactyly of toes 2 and 3, and upturned halluces (Fig. 3). His body hair was increased, and nonpitting edema was present in the lower limbs (Fig. 4). The testes were undescended. He had a hypotonic diplegia with increased deep tendon reflexes. The patient was not able to sit alone or stand; he had no vocalizations other than crying and showed no comprehension of language, but he listened selectively to speakers and made good eye contact. His ocular examination (including corneal diameters) was normal.

Dermatoglyphics

The patient had arches on both thumbs, and a total ridge count of 62 (midparent correlation, 0.76). His fa-

Fig. 1. Hypotonic face of patient, with almond-shaped eyes and apparently low-set ears.

Fig. 2. Adducted thumb.

ther had a total ridge count of 130, and his mother, 25 (right hand, 20 with a radial loop on the second finger; left hand, 5 with a radial loop on the second finger and arches on the first and third).

Examination Results

Results of laboratory examinations (ammonia, urinary amino acids and organic acids, blood lactate, pyruvate, acetate, beta-hydroxybutyrate, carnitine, vitamin E, cholesterol, 7-dehydrocholesterol, thyroid function tests, and muscle enzymes) were normal. Anti-HIV antibodies and a STORCH (syphillis, toxoplasma, rubella, cytomegalovirus, herpes) screen were negative. A karyotype study, DNA methylation study for Prader-Willi syndrome, EEG (electroencephalography), and EMG (electromyography) showed no abnormalities.

Brain Imaging

Brain CT was normal. Brain MRI, performed at age 5 months and again at 15 months, showed normal differentiation between white and gray matter with myelinization according to age, but also a mild symmetric enlargement of the lateral ventricles.

Muscle Biopsy

A muscle biopsy was performed because of hypotonia at age 19 months. Histochemistry was normal, but electron microscopy showed irregular-shaped and swollen mitochondriae in some muscle fibers. The mitochondrial function tests, including respiratory-chain enzymes and pyruvate dehydrogenase complex, were normal.

Follow-Up

The patient's motor development continues at a very slow pace, but at age 2 years there has been no language development.

DISCUSSION

Flexed and adducted thumbs occur in several syndromes, including distal arthrogryposis type I [Hall et al., 1982], whistling-face syndrome [Weinstein and Gorlin, 1969; Kousseff et al., 1982], congenital contractural arachnodactyly [Hall et al., 1982], congenital clasped thumbs [Fitch and Levy, 1975; Hall et al., 1982], ulnar drift syndrome [Stevenson et al., 1975], X-linked hydrocephalus [Howard et al., 1981], and MASA syndrome [Bianchine and Lewis, 1974]. A flexed and adducted thumb, sometimes with additional flexion of other fingers over the adducted thumb, is also described in cases of severe cortical damage producing spasticity of the extremities [Pinsky et al., 1965].

Adducted thumbs syndrome was first described by Christian et al. [1971] as a new genetic entity which could be differentiated, on a clinical basis, from other previously described syndromes. All 4 cases presented with arthrogryposis, microcephaly, abnormal ear place-

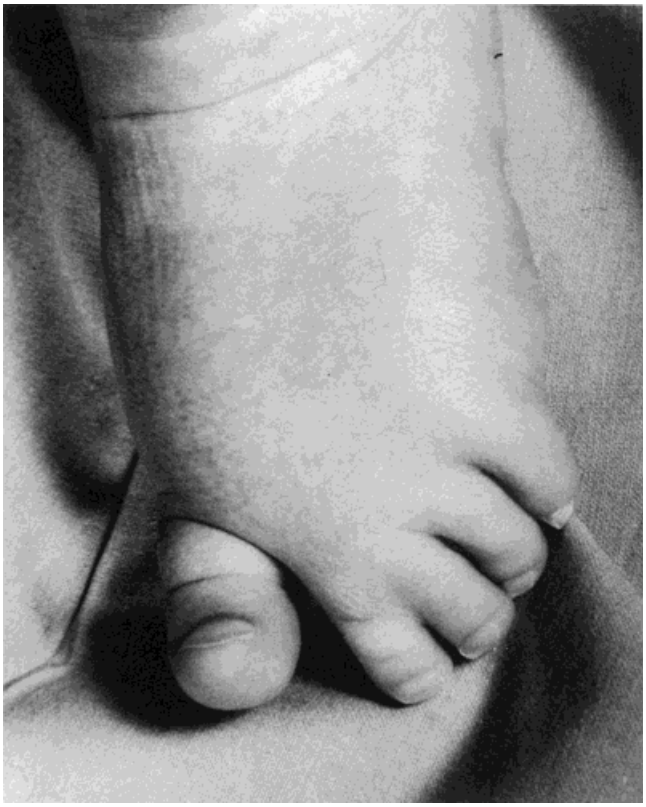

Fig. 3. Coxa valga, feet syndactyly, and upturned great toes.

Fig. 4. Nonpitting edema of the lower extremities.

ment, and difficulty swallowing. Craniostenosis, antimongoloid slanting of palpebral fissures, ophthalmoplegia, cleft palate, and fibrillations on electromyography were found in 3 of the 4 patients. The neuropathologic diagnosis of one autopsied patient was dysmyelination of a previously undescribed type, glial proliferation, and lipophilic plaques on the surface of the central nervous system. The syndrome was assumed to be due to a gene defect (such as point mutation and deletion) producing abnormal synthesis of a protein or lipid and consequently altered myelin synthesis.

Fitch and Levy [1975] described a new case which shared some of the clinical features described by Christian et al. [1971], with the exception of craniostenosis, antimongoloid slant, difficulty swallowing, and talipes equinovarus. The patient was mentally retarded, which was not reported in the previously described cases. Moderate hypotonia with normal deep-tendon reflexes was present.

Generalized hypotonia, a few spontaneous movements, and respiratory insufficiency leading to death at age 3 months were the most outstanding clinical features in the patient of Kunze et al. [1983]. A muscle biopsy showed great variation in fiber size, an increased number of centrally located nuclei, and increased interstitial tissue; no electron microscopic studies were performed. A nonspecific congenital myopathy was hypothesized, although neurogenic atrophy could not be discarded.

Our patient presents with the same clinical features reported in previously published cases of adducted thumbs syndrome, as summarized in the review of Kunze et al. [1983]. They include difficulty swallowing, microcephaly, structural palate anomalies, and abnormal ear placement. The only exception is talipes equinovarus, which was present in 8 of the reported cases but not in ours.

Mental retardation, muscular hypotonia, myopathic face, muscle abnormalities, oral secretions, and hirsutism were reported in the cited review [Kunze et al., 1983] as being present in some patients, and those findings were also positive in our case.

Early death occurred in 6 of the 9 patients, mostly as a consequence of respiratory infections secondary to swallowing difficulties. We assume that the gastrostomy performed in our patient has thus far prevented this fatal outcome.

Most of the clinical features in our patient, including cerebral atrophy, progressive microcephaly, severe mental retardation, and increased deep-tendon reflexes, can be related to abnormal development of the central nervous system. This differs from the case of Kunze et al. [1983], where the clinical findings suggested a severe congenital myopathy which could explain the presence of arthrogryposis with adducted thumbs, in a patient who was not microcephalic and whose mental development could not be evaluated because of early death.

Arthrogryposis, which was described in 8 of the adducted thumbs syndrome patients, can be related to severe fetal hypotonia of a neurogenic or myopathic origin. Since flexed and adducted thumbs are a frequent finding in arthrogryposis, it is not clear whether the adducted thumbs in the reported cases were an integral part of the arthrogryposis clinical picture, or a unique feature characterizing a separate syndrome. Our patient presents with adducted thumbs and no other joint contracture or deformation, which suggests that adducted thumbs are a main feature in the syndrome characterization.

X-linked MASA syndrome (mental retardation, adducted thumbs, shuffling gait, and aphasia) is due to a mutation on the L1 CAM (cell-adhesion molecule) gene on chromosome Xq28 [Jouet et al., 1994]. X-linked hydrocephalus and X-linked complicated spastic paraplegia also result from mutations on the same locus [Ruiz et al., 1995]. Male patients with adducted thumbs sequence, such as our patient, may represent other allelic mutations, thus extending the phenotypic spectrum of the cell-adhesion molecule gene.

In our opinion, the adducted thumbs sequence has not been thoroughly defined yet and is probably underdiagnosed and underreported, since clinicians may often interpret adducted thumbs in a developmentally delayed child as "cortical thumbs," even in the presence of hypotonia. The small group of patients reported so far seems to be heterogeneous, with considerable variability in their main findings. An accurate definition of this sequence will only be available with its characterization at the molecular level.

REFERENCES

Bianchine JW, Lewis RC Jr (1974): The MASA syndrome: A new heritable mental retardation syndrome. Clin Genet 5:298–306.

Christian JC, Andrews PA, Conneally PM, Muller JT (1971): The adducted thumbs syndrome. An autosomal recessive disease with arthrogryposis, dysmyelination, craniostenosis and cleft palate. Clin Genet 2:95–103.

Fitch N, Levy EP (1975): Adducted thumb syndromes. Clin Genet 8: 190–198.

Hall JG, Reed SD, Greene G (1982): The distal arthrogryposes: Delineation of new entities—Review and nosologic discussion. Am J Med Genet 11:185–239.

Howard FM, Till K, Carter CO (1981): A family study of hydrocephalus resulting from aqueduct stenosis. J Med Genet 18: 252–255.

Jouet M, Rosenthal A, Armstrong G, et al. (1994): X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. Nat Genet 7:402–407.

Kousseff BG, McConnachie P, Hydro TA (1982): Autosomal recessive type of whistling face syndrome in twins. Pediatrics 69:328–331.

Kunze J, Park W, Hansen KH, Hanefeld F (1983): Adducted thumb syndrome. Report of a new case and a diagnostic approach. Eur J Pediatr 141:122–126.

Majoor-Krakauer D, Weicker H (1981): Das "adducted-thumb syndrome," Poster-Session, 17. Tagung der Gesellschaft für Anthropologie und Humangenetik, Göttingen, 23.0–26.9.

Pinsky L, DiGeorge A, Harley R, Baird H (1965): Microphthalmos, corneal opacity, mental retardation and spastic cerebral palsy. An oculocerebral syndrome. J Pediatr 67:387–398.

Ruiz JC, Cuppens H, Legius E, Fryns JP, Glover T, Marynen P, Cassiman JJ (1995): Mutations in the L1-CAM in two families with X-linked complicated spastic paraplegia, MASA syndrome, and HSAS. J Med Genet 32:549–552.

Stevenson RE, Scott CI Jr, Epstein M (1975): Dominantly Inherited Ulnar Drift. BD: OAS XI (5):75–77.

Weinstein S, Gorlin RJ (1969): Cranio-carpo-tarsal dysplasia or the whistling face syndrome. Am J Dis Child 111:427–433.